29. (new) The method of claim1 wherein dietary intake of tryptophan is less than 1.44 grams.

REMARKS

Claim Status

Claims 1-24 are pending in the application. The Examiner has rejected claims 1-24. In response, Applicant has canceled claims 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 24. Applicant has amended claims 1,14, 15, 16, 17, 18, 19, 20, 21, 22, and 23. Applicant has added new claims 25, 26, 27, 28 and 29. Neither the amended claims nor the new claims contain new matter.

Claim Rejections - 37 CFR 1.75(c)

The Examiner has objected to claims 10-24 under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative. Applicant has eliminated all multiple dependent claims from the application. Applicant requests re-examination of the claims in light of the amendments.

Claim Rejections - 35 U.S.C. § 112

The Examiner has rejected claims 1-9 under 35 U.S.C. § 112, first paragraph, as failing to teach how to make and/or use the invention, and thereby failing to provide an enabling disclosure. In light of the Examiner's suggestion on page 10 (paper 7) to use a different word than "pharmacological", Applicant has substituted the word "effective amount" for the recited "pharmacological" in the relevant claims. *See e.g., See e.g., In re Halleck*, 442 F.2d 911(C.C.P.A. 1970) (discussed *infra* section 2(A); approving use of the term "effective amount"); I*n re Caldwell,* 50 C.C.P.A. 1464, 1469, 319 F.2d 254, 258 (1963) (discussed *infra* section 2(A); approving use of "effective amount"). Applicant requests re-examination of the claims in light of the amendments.

Claim Rejections - 35 U.S.C. § 102

The Examiner rejects claims 1-9 under 35 U.S.C. § 102 as being anticipated under the Merk Manual. Through the claim amendments, Applicant believes that the Examiner's concern regarding the Merck Manual has been overcome. *See e.g., In re Halleck*, 442 F.2d 911(C.C.P.A. 1970)(discussed *infra* section 2(A))(approving similarly worded claims to overcome Merck Manual). Applicant requests re-examination of the claims in light of the amendments.

Claim Rejections - 35 U.S.C. § 103

The Examiner maintained the obvious rejection of claims 1-9 under 35 U.S.C. § 103. Applicant respectfully requests Examiner to reconsider and withdraw of the rejections of record with respect to the obviousness rejection under 35 U.S.C. § 103.

It appears from page 11 (of paper 7) that the Examiner believes that Applicant's January 16, 2002 response to the obviousness rejection of first office action was not "directed to those actual elements included in the [obviousness rejection of the first office action]." In addition, it appears from page 11 (of paper 7) that the Examiner believes that Applicant's first response to the obviousness rejection was improperly directed toward "the verbiage of page 3 (of paper 4)...." Applicant apologizes for any confusion inadvertently created by the January 16, 2002 response. Applicant will attempt to re-state its response more clearly and respectfully requests that the examiner to reconsider the obvious rejection in light of the re-stated response.

1. **Applicant requests that the Examiner reconsider the obvious rejection because a *prima facie* case cannot be made when the prior art is unpredictable.**

In response to the first office action, Applicant did not present substantive argument in response to the rejection pursuant to 35 U.S.C. § 103 because Applicant responded on procedural grounds. Pursuant to MPEP 706.02(j), an applicant is not required to submit evidence or a substantive response until a prima facie case is made. *In Re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993)("In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness.

Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." (citations omitted)).

In this case, Applicant contends, and still contends, that the Examiner has not set forth a prima facie case of obviousness for the reasons described in Applicant's previous response dated January 16, 2002. "Obviousness cannot be predicated on what is unknown." *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). To establish a *prima facie* case of obviousness, "a reasonable likelihood of success must [] be found in the prior art." MPEP 2142, *Establishing a Prima Facie Case of Obviousness*. According to the MPEP, "at least some degree of predictability is required." MPEP 2143.02. In this case, the prior art cited by the examiner provides no degree of predictability. Therefore, no *prima facie* case can be established.

On page 3 of the first Office Action dated 7/27/2001 (paper 4), Examiner stated that "[t]he pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity." (emphasis supplied). Applicant cited the "verbiage of page 3 (of paper 4)" in support of the proposition that the relevant art is unpredictable. Applicant concedes that the "verbiage of page 3 (of paper 4)" was used by the examiner to support a rejection under 35 U.S.C. § 112. However, the fact that the "verbiage" was used in a §112 rejection does mean it is irrelevant with respect to a *prima facie* analysis under § 103. The predictability (or unpredictability) of the relevant art must remain the same under §103 as it does under §112. The relevant art cannot be "unpredictable" when rejecting a claim under §112, while at the same time being predictable enough to establish a *prima facie* case of obviousness under § 103. Unpredictable under §112 means unpredictable under §103. The "verbiage of page 3 (of paper 4)" affirmatively states that the relevant art is "unpredictable"—at least with respect to a §112 rejection. Without predictability, the *prima facie* case of obviousness under § 103 fails. *See* MPEP 2143.02.

In addition, the prior art relied upon by the Examiner further reinforces the conclusion that the prior art is unpredictable. Not only did Tang et. al concede that the data they gathered does not necessarily support a conclusion that niacin had any effect at

all on immune function, but Tang et. al admit that, as far as they can tell, niacin may be nothing more than a marker of B-group vitamins:

> Since intakes of B-group vitamins are highly **intercorrelated**, further research is needed to determine if one or more of these nutrients is related to HIV-1 disease progression. Under these circumstances, **niacin may represent a marker** of overall intake of B-group vitamins **rather that having any direct effect** on immune function.

(Tang et. al, at 948) (emphasis supplied).

In addition, the study conducted by Tang, et al was based on patient responses to questionnaires. Thus, the Tang study was observational not experimental. Tang, et al. expressly highlight several limitations to their study, including that the "food frequency questionnaire" has not been validated in any HIV-1 seropositive population (Tang et. al, at 950). More importantly, though, Tang, et al. admit that dietary changes of the study's participants may not have any effect at all on disease progression. *Id.* In fact, dietary changes of the participants may be "a result of disease progression, rather than a cause." *Id.* At best, Tang, et. al merely claim that their "findings appear to have some biological plausibility." *Id.*

Similarly, the *in vivo* teaching of Murray et al. is similarly unpredictable. Murray et al expressly state that their extrapolation of *in vitro* data was merely speculation and hypothesis that could only be confirmed by *in vivo* data:

> **We speculate** that NAm works to inhibit one or more ADP-ribosylation steps which might otherwise deplete the infected cell of NAD.
>
> ...
>
> **If our original hypothesis** that HIV induces a pellagroid state **is correct**...
>
> ...
>
> **... if confirmed on an *in vivo* level.**

Murray et al, at 958-59 (emphasis supplied).

Thus, not only is the pharmaceutical art unpredictable as a whole, the prior art relied upon by the Examiner expressly concedes that their conclusions were speculation

and hypothesis that needed further research and verification before they could be relied upon. Because the prior art fails the degree of predictability required by MPEP § 2143.02 and because—as the Examiner has pointed out—the relevant prior art is "unpredictable", the Examiner cannot establish a *prima facie* case of obviousness. As such, the obviousness rejection must be withdrawn.

2. In the event that the Examiner does not withdraw his objection on *prima facie* grounds, the Examiner should withdraw the § 103 rejection because claims 1-24 are not obvious in light of the teachings of Tang et. al and Murray et. al.

A. Applicant's invention is directed to increasing systemic tryptophan not anti-HIV therapy; using niacin to increase systemic tryptophan is not in the prior art

Examiner's states that the prior art "teaches anti-HIV therapy by administering elevated levels of niacin." (page 11 of paper 7) In addition, Examiner states that the prior art reports "slowing the progression of the disease and reducing symptomology." Applicant's invention is different. Applicant has discovered a method of increasing systemic tryptophan of humans infected with a retrovirus and in need of an increase in systemic tryptophan even though their diet already contains the RDA (recommended daily dose) of niacin and tryptophan. Applicant's invention is new, useful and non-obvious. None of the Examiner prior art even hints at such an invention.

Examiner also states that Applicant's invention is "an inherent characteristic of the prior art." (*See* page 9, citing *Swinehart*). Examiner's view of the inherency doctrine is overbroad. An "inherent characteristic" necessarily flows from the teachings of the prior art." MPEP § 2112, (Section titled *Examiner Must Provide Rationale of Evidence Tending to Show Inherency*)(citing *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(empahsis in original). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish inherency.]" *In Re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993)(quoting *In re Oelrich,* 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). In similar cases involving a novel application for a common substance, claims directed to the novel application are not obvious unless they necessarily

flow from the prior art. *See e.g., In re Halleck* 422 F.2d 911 (C.C.P.A. 1970); *In re Caldwell*, 50 C.C.P.A. 1464, 1468-69, 319 F.2d 254, 257-58 (1963).

In *Halleck*, a case remarkably similar to this case, the applicant sought method claims directed to "animal feed and an effective amount of a peristalsis-regulating substance contained therein for growth stimulation." 422 F.2d at 912. The Merck "reference disclosed use of the parasympatholytic agents for relaxing smooth muscles," in similar amounts as claimed by the applicant. *Id.* at 912. The Examiner denied the claims as inherently obvious because Merck disclosed administration of the same substance in similar amounts as the claim at issue, and was thus "inherently" disclosed by Merck. *Id.* In addition, the examiner rejected the claims as obvious in light of Goodman in view of a Journal Article and Merck because those references suggested an increased caloric intake when intestinal time is increased. *Id.* In light of these references, the Examiner concluded that it would be "obvious to increase intestinal time in order to improve utilization of the feed and growth." *Id.*

The Court of Customs and Patent Appeals ("CCPA") rejected both of the examiner's arguments because:

> Appellant's invention is not merely a composition comprising an animal feed and a peristalsis-regulating substance nor a method of administering a peristalsis-regulating substance to animals. Rather, what is alleged to be **novel and unobvious is the discovery that a peristalsis-regulating substance will stimulate animal growth.** No prior art suggests this.

Id. (emphasis supplied). The CCPA found that the claims were not obvious because the prior art of record was silent with respect to stimulating animal growth by administration of peristalsis-regulating substances. *Id.* at 914. In this case, the prior art is silent with respect to increasing systemic tryptophan with the use of niacin. As such, the claims are not inherently obvious.

In *Caldwell*, another case remarkably similar to this case, the applicant sought method claims directed to "supplying an effective amount of aspirin for growth stimulation." *Id.*, 50 C.C.P.A. at 1465, 319 F.2d at 255. The Court of Customs and Patent Appeals ("CCPA") noted that while aspirin had been administered to children and

MARKED UP VERSION OF AMENDED CLAIMS

1. (twice amended) A method [for treating a patient infected with a retrovirus, which comprises the step of administering a daily pharmacological dose of niacin to the patient infected with a retrovirus] of increasing systemic tryptophan comprising the administration of an effective amount of niacin for increasing systemic tryptophan to a patient in need of an increase in systemic tryptophan wherein the patient is infected with a retrovirus and wherein the patient has a diet that includes at least the RDA [recommended daily allowance] of niacin and tryptophan.

2. **[Deleted]** (Once Amended) A method for treating retrovirus-induced metabolic changes, which comprises the step of administering a daily pharmacological dose of niacin to a patient with retrovirus-induced metabolic changes.

3. **[Deleted]** (Once Amended) A method for treating a patient infected with HIV, which comprises the step of administering a daily pharmacological dose of niacin to the patient infected with HIV.

4. **[Deleted]** (Once Amended) A method for treating HIV-induced metabolic changes, which comprises the step of administering a daily pharmacological dose of niacin to a patient with HIV-induced metabolic changes.

5. [**Deleted**] (Once Amended) A method for treating retrovirus-induced metabolic changes in a patient's systemic tryptophan levels, which comprises the step of administering a daily pharmacological dose of niacin to the patient with retrovirus-induced metababolic changes in the patient's tryptophan levels.

6. [**Deleted**] (Once Amended) A method for treating HIV-induced metabolic changes in a patient's systemic tryptophan levels, which comprises the step of administering a daily pharmacological dose of niacin to the patient with HIV-induced metabolic changes in the patient's systemic tryptophan levels.

7. [**Deleted**] (Once Amended) A method for treating the depletion of tryptophan in a retrovirus-infected patient, which comprises the step of administering a daily pharmacological dose of niacin to the retrovirus-induced patient with depleted levels of tryptophan.

8. [**Deleted**] (Once Amended) A method for treating the depletion of tryptophan in an HIV-infected patient, which comprises the step of administering a daily pharmacological dose of niacin to the HIV-infected patient with depleted levels of tryptophan.

9. [**Deleted**] (Once Amended) A method for repleting nicotinamide nucleotide precursors, which comprises the step of administering a daily pharmacological dose of niacin to a patient needing repletion of nicotinamide nucleotide precursors.

10. [**Deleted**] The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to prevent retrovirus-induced metabolic changes in systemic tryptophan concentrations.

11. [**Deleted**] The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to slow down the rate of retrovirus-induced metabolic changes in systemic tryptophan concentrations.

12. [**Deleted**] The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to stop the rate of retrovirus-induced metabolic changes in systemic tryptophan concentrations.

13. [**Deleted**] The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to increase a patient's level of plasma tryptophan.

14. (once amended) [A] The method [as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount is greater than 100 milligrams per day.

15. (once amended) [A] The method [as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount is approximately 3 grams per day.

16. (once amended) [A] The method [as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount exceeds the standard recommended daily amounts for coenzyme activity.

17. (once amended) [A] The method [of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount exceeds amounts normally obtainable with routine diet and supplement practices.

18. (once amended) [A] The method [as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount exceeds the RDA [recommended daily allowance] of niacin.

19. (once amended) [A] The method [as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount is sufficient to raise the intracellular levels of nicotinamide adenine dinucleotide [NAD] in persons with HIV infection.

20. (once amended) [A] The method [as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount is sufficient to replete nicotinamide nucleotide precursors [NAD].

21. (once amended) [A] The method [of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount of niacin is administered to persons with HIV and other co-infections.

22. (once amended) [A] The method [as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount of niacin is administered in combination with antiviral medications [such as] selected from the group consisting of reverse transcriptase inhibitors, and protease inhibitors.

23. (once amended) [A] The method [as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose] of claim 1 wherein the effective amount is administered in combination with other treatments for HIV infection to improve the metabolic status of an infected patient.

24. **[Deleted]** A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is sufficient to inhibit new virus production.

rats and the growth rates measured, the claims were not obvious because nothing in the prior are suggested **the use** claimed by the applicant:

> Although aspirin is practically our national drug, it does not appear from anything on the record that its use as a growth promoter for any animal, human or otherwise, has ever been even suggested. As for the reference, we are in complete agreement with the appellant, whose brief states: `It seems pretty clear that the Gross reference stands for, and suggests, only one thing as far as the present case goes. That is, that feeding aspirin to children and rats over prolonged periods does not interfere with or retard growth of these two species of animals. As far as aspirin goes, this is the only teaching that can be derived from the reference.'"

Caldwell, 50 C.C.P.A. at 1466, 319 F.2d at 256. **The CCPA went on to say that the "real novelty" is "stimulating the growth of ruminants, poultry, or swine by feeding them aspirin for that purpose."** *Id.* 50 C.C.P.A. at 1468, 319 F.2d at 257 (emphasis supplied). "We therefore disagree...that the "real novelty" must reside in the amount of aspirin fed, rather than in the feeding of aspirin for the stated purpose." *Id.*

In this case, Examiner claims that Applicants invention is not patentable because it is a "mere recitation of a newly discovered function or property." (*See* page 9 of paper 7). Examiner's interpretaion of the "inherency" doctrine goes too far. Just like the applicant in both *Halleck* and *Caldwell,* Applicant here claims a novel purpose for a known substance: administering an effective amount of niacin to increase systemic tryptophan of humans infected with a retrovirus and in need of an increase in systemic tryptophan even though their diet already contains the RDA (recommended daily dose) of niacin and tryptophan. Nothing in the prior art suggests as much. The mere fact that others have administered high doses of niacin to patients with HIV and hypothesize that it may be "biologically plausible" that high doses of niacin could slow the onset of HIV does not render obvious Applicant's claim to a wholly different purpose. Applicant respectfully requests that the obvious rejection be withdrawn.

B. In the event that Examiner does not withdraw his obvious rejection, Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination an increase in systemic tryptophan necessarily follows from the teachings of Tang et. al and Murray et. al.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art." MPEP § 2112, (Section titled *Examiner Must Provide Rationale of Evidence Tending to Show Inherency*)(citing *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(empahsis in original). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish inherency.]" *In Re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993)(quoting *In re Oelrich,* 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

In this case, the Examiner appears to claim that an increase in systemic tryptophan is an "inherent characteristic" that flows from teachings of Tang and Murray. An increase in systemic tryptophan, however, cannot be said to necessarily flow from the teachings of Tang and Murray. The teachings of Tang concede that the observational data they gathered did not necessarily support a conclusion that niacin has any effect at all:

> Since intakes of B-group vitamins are highly **intercorrelated**, further research is needed to determine if one or more of these nutrients is related to HIV-1 disease progression. Under these circumstances, **niacin may represent a marker** of overall intake of B-group vitamins rather that having any direct effect on immune function.

Tang et. al, at 948 (emphasis supplied). Tang, et. al concede that their findings have, at best, only "some biological plausibility." Tang et. al, at 948. More importantly, though, nothing in Tang et al suggests that niacin increases systemic tryptophan levels.

Similarly, an increase in systemic tryptophan cannot be said to necessarily flow from the *in vivo* teaching Murray et al. Murray et al evaluated nicotinamide as an inhibitor of HIV *in vitro*.

If the Examiner does not withdraw the objection, Examiner must provide a basis in fact and/or technical reasoning to reasonably support that increased systemic tryptophan necessarily flows from the teachings of Tang et al and Murray et al as required by MPEP § 2112.

Conclusion

Applicant kindly asks for entry of claims 1,14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28 and 29. Applicant now believes that the application is now in condition for allowance and kindly asks the Examiner for reconsideration thereof.

Respectfully submitted,

Date: 9/23/02

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